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ORIGINAL ARTICLE

Healthcare utilization and direct medical cost in the years during and after cancer diagnosis in patients with type 2 diabetes mellitus

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ABSTRACT

Aims/Introduction: There is uncertainty about the direct medical costs of type 2 diabetes patients with cancers.

Materials and Methods: A population-based retrospective cohort of 99,915 type 2 diabetes patients from the Hong Kong Hospital Authority between 2006 and 2017 was assembled. A total of 16,869 patients who had an initial cancer diagnosis after type 2 diabetes diagnosis were matched with 83,046 patients without cancer (controls) using a matching ratio of up to one-to-five propensity score-matching method. Patients were divided into four categories according to life expectancy. Healthcare service utilization and direct medical costs during the index year, subsequent years and mortality year were compared between patients with and without cancer in each category.

Results: Medical costs of cancer patients in the index year ranged from $US27,533 for patients who died in <1 year to $US11,303 for those survived >3 years. Cancer patients had significantly greater expenditures than controls in the index year (all $P < 0.001$) and subsequent years ($US4,569 vs $US4,155, $P < 0.001$). Cancer patients also had greater costs in the year of death, and the difference was significant for patients who survived >3 years after the index year ($US32,558 vs $US28,260). For patients in both groups, patients who survived >3 years had significantly lower costs than those who died in <1 year. Costs incurred in the mortality year were greater than those in the index year and subsequent years. Hospitalization accounted for >90% of the medical costs for both groups in the mortality year.

Conclusions: Type 2 diabetes patients with cancers incurred greater medical costs in the diagnosis, ensuing and mortality years than type 2 diabetes patients without cancers.

INTRODUCTION

Cancer causes a tremendous disease burden worldwide[1]. As the leading cause of death globally, cancer accounted for 18.1 million new cases and 9.6 million deaths in 2018[2]. The incidence of cancer has increased over the years, and its upward trend is partly due to the rising prevalence of risk factors, such as diabetes, obesity and other lifestyle factors[1]. An increasing number of studies confirm that type 2 diabetes is associated with an increased risk of cancer and cancer mortality[3–8]. Indeed, patients with type 2 diabetes have a higher incidence across all cancer types, with a risk ratio of 1.23 for Asian patients and 1.15 for non-Asian patients[9]. For hepatocellular carcinoma, in particular, the increased risk among patients with type 2 diabetes reaches 131%[10]. In view of the strong link between diabetes and the incidence of cancer, a joint consensus statement convened by the American Diabetes Association and the American Cancer Society stated that type 2 diabetes patients are more likely to develop cancers in the liver, pancreas, endometrium, colon and rectum, breast and bladder, although they are less likely to develop prostate cancer[11].

The economic burden of cancers is tremendously heavy from either a macroscopic or an individual perspective[12–14]. The

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estimated direct medical costs and indirect costs resulting from a loss of productivity among cancer patients have reached $US2 trillion globally[15]. At an individual level, up to $81,655 was incurred in the post-diagnosis period for each cancer patient who died within 1 year[16]. Of note, oncology patients who died within 1 year after diagnosis tend to have higher medical costs than those who survived beyond 1 year in the post-diagnosis periods[16]. This is probably because the cost of treating cancer increases with the advancement of the disease, as extra treatments, intensive care and expensive drugs are given during the end-of-life care[17,18].

In recent years, the increasing use of computer simulation models of diabetes progression in clinical decision-making processes has addressed clinical questions with long-term simulated results[19]. Although diabetes-related complications, including cardiovascular diseases, retinopathy, nephropathy and amputation, have been widely included in the existing economic evaluations of interventions for type 2 diabetes, none of them considered cancers as one of the modeled complications[20], even though the guidelines for economic models of diabetes advocate a compression of multiple diabetes complications[21]. As type 2 diabetes is associated with an increased risk of cancer and the burden of cancer is heavy, diabetes economic models could be further refined by introducing cancers. However, no known studies have measured the direct medical costs of type 2 diabetes patients coexisting with cancer, and thus it remains a great challenge to incorporate cancer into the model.

This population-based cohort study aimed to: (i) examine the direct medical costs of type 2 diabetes patients with cancers in the year of diagnosis, ensuing years and the year of death by their life expectancies; (ii) compare the costs of type 2 diabetes patients with and without cancers; and (iii) assess the impact of baseline covariates of patients on direct medical costs.

METHODS

Study design and population

A retrospective propensity score-matched cohort study was carried out. Patients who used the Hong Kong Hospital Authority (HA) healthcare services between January 2006 and December 2017 were identified from the HA Clinical Management System. Disease diagnoses were identified according to the International Classification of Diseases, Ninth Revision, Clinical Modification and International Classification of Primary Care, Second Edition (Table S1). A 1-year screening period was used to exclude patients whose cancer diagnosis was made in or before the year 2006. Patients who had cancer diagnosis on or after the onset date of type 2 diabetes were assigned to the cancer group. The index date was defined as the date of the first occurrence of a cancer event during the study period. To fully use the large pool of non-cancer patients, a group of type 2 diabetes patients without a recorded cancer diagnosis during the observation period was matched in a ratio up to one-to-five using caliper propensity score matching.

All procedures carried out in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Ethics approval of this study was granted by the institutional review board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (Ref No. UW 16-1018).

Outcomes

Primary outcomes were the direct medical costs of patients in the cancer and control group incurred in the index year, ensuing years and the last year of life. For patients in the cancer group, direct medical costs were further measured by tumor sites.

Secondary outcomes included the pattern of use of healthcare services by type 2 diabetes patients with and without cancer, and the impacts of baseline characteristics of patients on medical costs.

Estimation of direct medical costs

The dates and types of healthcare service used by patients in both groups during the observation period were retrieved. Cost items included general outpatient clinic visits, specialist outpatient clinic (SOPC) visits, accident and emergency visits, applied health professional visits, and length of stay in a general ward, in an intensive care unit, in a coronary care unit and in a high dependency unit. The unit cost of each type of healthcare service was extracted from the public charges to non-eligible persons listed in the 2017 Government Gazette and HA Ordinance (Chapter 113; Table S2)[22]. The pegged exchange rate of $US1 = $HK7.80 was used to convert Hong Kong dollars to US dollars[23]. The annual direct medical costs of each patient were calculated by summing up the unit cost of each healthcare service multiplied by the frequency of use of the respective service.

Patients in both groups were divided into four categories by their life expectancies after the index year, including those who: (i) died within 1 year after the index date (category 1); (ii) survived >1 year, but died within 2 years after the index date (category 2); (iii) survived >2 years, but died within 3 years after the index date (category 3); and (iv) survived >3 years after the index date (category 4). Costs in the index year were the costs incurred from the index date to 1 year after the index date, whereas the costs incurred in the mortality year were the costs incurred from 1 year before the mortality date to the date of death. Of note, costs in the index year of patients in category 1 were also the costs of the mortality year. To avoid repeated calculations, costs incurred beyond the index year were regarded as the costs in the mortality year for patients in category 2. Only patients in category 4 had the costs in the ensuing years, which were the mean value of the costs incurred between 1 year after the index date and 1 year before the death date

(for patients who died during the observation period) or the mean value of the costs incurred between 1 year after the index date and the last observation date (for patients who survived during the whole observation period).

Baseline covariates

The baseline covariates included sex (male, female), age (≤75 years, >75 years), Charlson Comorbidity Index (CCI; ≤3, 4–6, ≥7), laboratory parameters (including glycated hemoglobin, systolic blood pressure, diastolic blood pressure, low-density lipoprotein cholesterol, total cholesterol, high-density lipoprotein cholesterol, serum creatinine, triglyceride and fasting glucose), duration of type 2 diabetes (≤5 years, >5 years), presence of comorbidities (including mental health problems, hyperlipidemia, obstructive sleep apnea, gallbladder disease, musculoskeletal and chronic orthopedic disorders, end-stage renal disease and hypertension), and the use of insulin, oral antidiabetic drugs, antihypertensive drugs and lipid-lowering agents.

Statistical analysis

Propensity score-matching method

Multiple imputation by chained equations was used to address the absence of baseline data[24]. Glycated hemoglobin, systolic blood pressure, diastolic blood pressure, low-density lipoprotein cholesterol, total cholesterol, high-density lipoprotein cholesterol, serum creatinine, triglyceride and fasting glucose were imputed by demographics (sex and age), body mass index, CCI, history of comorbidities (including mental health problems, hyperlipidemia, obstructive sleep apnea, gallbladder diseases, musculoskeletal and chronic orthopedic disorders, and hypertension) and the use of medications (including insulin, oral antidiabetic drugs, antihypertensive drugs and lipid-lowering drugs). Missing percentages for glycated hemoglobin, systolic blood pressure, diastolic blood pressure, low-density lipoprotein cholesterol, total cholesterol, high-density lipoprotein cholesterol, triglyceride and fasting glucose were 3.97%, 9.34%, 9.42%, 10.12%, 9.53%, 9.97%, 9.97% and 10.62%, respectively. Model parameters estimated from multiple imputed data were used to obtain multiple imputation linear predictions by applying Rubin's combination rules observation-wise to the completed data predictions[25]. The obtained predictions were then used in propensity score matching. Each patient's propensity score was computed by multivariable logistic regression adjusting for baseline clinical parameters and covariates. Command "calipmatch" in Stata (StataCorp LP, College Station, TX, USA) with a caliper width of 0.05 was used to match cancer patients with controls on a one-to-five basis.

The baseline characteristics of patients before and after matching were presented by frequencies with percentages for categorical variables and means with standard deviation (SD) for continuous variables in a table. Independent *t*-tests or χ^2-tests were used to determine if there were significant differences between cancer and non-cancer patients. Standard mean difference, a statistic less sensitive to sample size, was calculated for each characteristic. A standard mean difference of <0.2 showed that the baseline characteristics between cancer patients and controls were well balanced[26].

Generalized linear models

Generalized linear models with log link and gamma distribution were used to explore the effects of patient covariates on direct medical costs. Generalized linear models were constructed separately for each category. Multipliers (exponential value of coefficients), corresponding 95% confidence intervals (CIs) and *P*-values for each covariate were reported.

All statistical analysis was carried out with Stata 13.1 (StataCorp LP). All significance tests were two-tailed, and a *P*-value <0.05 was statistically significant.

RESULTS

Patient characteristics

A total of 16,869 and 83,046 eligible cancer and control patients, respectively, were included in this analysis (Figure S1).

Table 1 summarizes the baseline characteristics of patients before and after the propensity score matching. The baseline characteristics of the cancer and control patients were well balanced (Figure S2). There were 4,811, 1,377, 725 and 9,956 cancer patients with a median follow-up duration of 3, 16, 29 and 41 months in categories 1–4, respectively. There were 2,795, 2,752, 2,575 and 74,924 control patients in categories 1–4, respectively. The median follow-up duration of the controls was 5, 17, 29 and 47 months in categories 1–4, respectively.

Utilization of healthcare services

Table 2 summarizes the use of healthcare services by patients in the cancer and control groups. Notably, the SOPC was the most frequently used healthcare service by all categories, apart from cancer patients' use of inpatient services. The frequency of SOPC visits by cancer patients ranged from 5.28 to 15.76 times, whereas that of control patients was less than five times across the four categories. Cancer patients had more SOPC visits than controls within the same category. Accident and emergency and allied health professional admissions tended to be more frequent for cancer patients than control patients during the observation period. However, the frequency of visits to general outpatient clinics by patients in the cancer and control groups was similar.

Compared with controls in the same category, cancer patients spent approximately 10 additional nights in general wards in the index year and three extra nights in general wards in the mortality year. However, both cancer and control patients in categories 1–4 spent less than one night in intensive care unit, coronary care unit and high dependency unit wards.

Direct medical costs

Figure 1 shows the mean direct medical costs of cancer and control patients in the index year, subsequent years and the mortality year. For patients in category 1, the direct medical

Table 1 | Baseline characteristics of patients in the cancer group and matched control group

Characteristics	Before matching	After 1-to-5 propensity score matching			
	Cancer patients (*n* = 21,327)	Cancer patients (*n* = 16,869)	Matched control patients (*n* = 83,046)	*P*-value	SMD†
Demographic					
Female, *n* (%)	10,130 (47.5)	8,249 (48.9)	41,523 (50.0)	0.013*	0.021
Mean age, years (SD)	76.70 (10.72)	76.83 (10.33)	76.81 (6.98)	0.714	0.003
Clinical parameters					
Mean HbA1c, % (SD)	7.11 (1.35)	7.08 (1.29)	7.08 (1.24)	0.719	0.003
Mean fasting glucose, mmol/L (SD)	7.38 (2.44)	7.33 (2.34)	7.32 (2.37)	0.191	0.004
Mean oral glucose tolerance test, mmol/L (SD)	9.53 (4.36)	9.57 (4.46)	9.68 (5.20)	0.191	0.022
Mean SBP, mmHg (SD)	133.61 (18.49)	133.78 (18.43)	134.26 (16.98)	0.002*	0.027
Mean DBP, mmHg (SD)	71.79 (10.78)	71.63 (10.69)	71.57 (10.14)	0.460	0.006
Mean total cholesterol, mmol/L (SD)	4.26 (1.02)	4.26 (0.98)	4.27 (0.91)	0.100	0.014
Mean HDL-C, mmol/L (SD)	1.17 (0.34)	1.19 (0.34)	1.20 (0.32)	0.003*	0.026
Mean TC/HDL-C ratio (SD)	3.89 (1.63)	3.81 (1.37)	3.76 (1.18)	<0.001*	0.038
Mean LDL-C, mmol/L (SD)	2.42 (0.86)	2.41 (0.85)	2.41 (0.77)	0.988	<0.001
Mean triglyceride, mmol/L (SD)	1.47 (0.88)	1.46 (0.84)	1.46 (0.82)	0.570	0.005
Mean serum creatinine, μmol/L (SD)	104.02 (90.47)	102.45 (89.32)	102.61 (73.62)	0.808	0.002
Mean eGFR, mL/min/1.73 m^2 (SD)	72.79 (28.50)	73.03 (27.96)	68.60 (53.39)	<0.001*	0.104
Comorbidities					
Mean duration of T2DM, years (SD)	4.79 (3.22)	5.09 (3.15)	5.07 (2.96)	0.401	0.007
Insulin used, *n* (%)	4,180 (19.6)	3,988 (18.7)	15,197 (18.3)	0.201	0.011
Oral antidiabetic drugs ever used, *n* (%)	13,009 (61.0)	10,594 (62.8)	51,405 (61.9)	0.028*	0.019
History of hypertension, *n* (%)	17,552 (82.3)	14,187 (84.1)	69,426 (83.6)	0.084	<0.001
Antihypertensive drugs ever used, *n* (%)	16,870 (79.1)	13,647 (80.9)	65,606 (79.0)	<0.001*	0.046
History of hyperlipidemia, *n* (%)	9,832 (46.1)	8,097 (48.0)	39,613 (47.7)	0.542	0.005
Lipid lowering agents ever used, *n* (%)	10,919 (51.2)	9,042 (53.6)	43,433 (52.3)	0.003*	0.025
History of mental health problems, *n* (%)	512 (2.4)	405 (2.4)	2,076 (2.5)	0.247	0.010
History of obstructive sleep apnea, *n* (%)	1,088 (5.1)	860 (5.1)	4,235 (5.1)	0.776	0.002
History of gallbladder disease, *n* (%)	981 (4.6)	759 (4.5)	3,820 (4.6)	0.713	0.003
History of musculoskeletal and chronic orthopedic disorders, *n* (%)	4,820 (22.6)	3,964 (23.5)	19,931 (24.0)	0.191	0.011
Charlson Comorbidity Index, *n* (%)				<0.001*	0.098
≤3	130 (0.61)	118 (0.7)	914 (1.1)		
4–6	18,687 (87.62)	16,565 (98.2)	81,800 (98.5)		
≥7	2,508 (11.76)	186 (1.1)	332 (0.4)		

DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; SD, standard deviation; T2DM, diabetes mellitus; TC, total cholesterol. *Significant difference (*P*-value <0.05) detected by independence *t*-tests or by χ^2-tests. †Standardized mean difference (SMD) <0.200 indicates the balance of baseline covariates.

Table 2 | Mean number of healthcare utilization (visits and length of stays) with standard deviation of cancer and control patients

Patients	Year	*n*	GOPC	SOPC	A&E	Allied health	Hospital length of stay	
							General ward	ICU, CCU and HDU
Cancer patients								
Category 1	Index year	4,811	0.75 (0.04)	5.28 (0.17)	2.53 (0.06)	0.22 (0.03)	38.08 (0.98)	0.45 (0.08)
Category 2	Index year	1,377	2.72 (0.15)	15.76 (0.45)	2.96 (0.17)	0.76 (0.13)	34.79 (2.15)	0.38 (0.08)
	Mortality year	1,377	0.85 (0.09)	5.32 (0.29)	2.35 (0.12)	0.22 (0.06)	30.11 (1.66)	0.27 (0.13)
Category 3	Index year	725	3.01 (0.22)	14.79 (0.60)	1.64 (0.14)	0.58 (0.12)	22.22 (2.21)	0.47 (0.15)
	Mortality year	725	2.14 (0.18)	11.55 (0.54)	3.58 (0.20)	0.39 (0.13)	41.43 (2.73)	0.28 (0.15)
Category 4	Index year	9,956	3.43 (0.06)	11.46 (0.15)	1.07 (0.03)	1.12 (0.07)	12.83 (0.41)	0.24 (0.03)
	Subsequent years	8,256	3.56 (0.07)	7.77 (0.12)	0.95 (0.04)	0.82 (0.07)	4.33 (0.03)	0.04 (0.01)
	Mortality year	1,138	2.15 (0.16)	10.01 (0.41)	3.71 (0.17)	0.51 (0.11)	42.71 (2.51)	0.82 (0.41)
Control patients								
Category 1	Index year	2,795	0.89 (0.08)	2.05 (0.11)	2.33 (0.08)	0.13 (0.03)	26.50 (1.31)	0.97 (0.17)
Category 2	Index year	2,752	2.30 (0.11)	4.56 (0.16)	2.15 (0.10)	0.35 (0.07)	20.68 (1.33)	0.26 (0.07)
	Mortality year	2,752	0.93 (0.08)	1.95 (0.10)	2.28 (0.08)	0.14 (0.03)	27.23 (1.32)	0.93 (0.16)
Category 3	Index year	2,575	2.51 (0.11)	4.43 (0.16)	1.56 (0.10)	0.39 (0.08)	11.70 (0.97)	0.12 (0.04)
	Mortality year	2,575	1.80 (0.10)	4.32 (0.16)	3.56 (0.12)	0.29 (0.05)	39.07 (1.72)	0.90 (0.19)
Category 4	Index year	74,924	3.65 (0.02)	3.02 (0.02)	0.69 (0.01)	0.46 (0.02)	3.16 (0.09)	0.05 (0.01)
	Subsequent years	64,504	3.36 (0.02)	3.41 (0.03)	0.90 (0.01)	0.48 (0.02)	4.78 (0.09)	0.05 (0.00)
	Mortality year	8,990	1.63 (0.05)	3.83 (0.08)	3.53 (0.06)	0.29 (0.03)	38.46 (0.91)	0.60 (0.08)

Category 1: patients die in the index year; category 2: patients die in the second year after the index date; category 3: patients die in the third year after the index date; category 4: patients survive >3 years after the index date. A&E, accident and emergency department; CCU, coronary care unit; GOPC, general outpatient clinic; HDU, high dependency unit; ICU, intensive care unit; SOPC, specialist outpatient clinic.

costs of cancer and control patients in the index year were $US27,533 and $US21,043, respectively ($P < 0.001$). Hospitalization accounted for the largest proportion (>95%) of the direct medical costs for both groups. Cancer patients in category 2 had higher medical costs than control patients in both the index year ($US26,988 vs $US15,542, $P < 0.001$) and the mortality year ($US21,790 vs $US21,343, $P = 0.594$). Similarly, cancer patients in category 3 had higher costs in the index year ($US18,695 vs $US9,121, $P < 0.001$) and the mortality year (US$30,433 vs US$29,608, $P = 0.534$), but the difference was not significant in the mortality year. For patients in category 4, the medical costs of cancer patients were significantly higher than those of controls in the index year, subsequent years and the mortality year (all $P < 0.001$). Compared with patients in other categories, patients in category 4 incurred less expenditure in hospitalization in the index year. However, the costs of hospitalization, again, were in excess of 90% of the total medical costs in the mortality year for patients in both the cancer and control groups. Of note, patients with longer remaining life expectancies had lower medical costs in the index year.

We further grouped the costs incurred in the index year and in the mortality year for patients in all four categories, and compared their annualized mean costs across patients in the four categories and between the two groups (Figure S3). Cancer patients in all four categories had significantly greater medical costs in the index year than in the mortality year (all $P < 0.001$). In group comparisons, patients in category 2, more of whom had aggressive cancers with high mortality rates (e.g., cancers in digestive organs and unspecified sites), had the highest medical costs; whereas patients in category 4, among whom there are fewer patients with aggressive cancers, had the lowest.

The mean direct medical costs of cancer patients in the index year, subsequent years and mortality year are shown by tumor sites in Table 3. The direct medical costs of patients in category 1 ranged from $US24,478.15 (SD $US1,023.28) in patients with cancers in other and unspecified sites to $US42,066.32 (SD $US8,380.46) for patients with cancers of the lip, oral cavity and pharynx. The patients in category 2 with cancers in lymphatic and hematopoietic tissue had the highest costs in the diagnosis year ($US33,762.93, SD $US8,612.39), and patients with cancers of the lip, oral cavity and pharynx had the highest costs in the mortality year ($US28,072.39, SD $US8,233.23). Patients in category 3 with lymphatic cancers and leukemia had the highest direct medical costs in both the diagnosis year ($US28,706.56, SD $US12,983.92) and the mortality year ($US39,598.94, SD $US12,817.13). Finally, the medical costs of patients in category 4 in the diagnosis year ranged from $US7,133.32 (SD $US472.55) to $US18,429.11 (SD $US2,839.51); the direct medical costs in the subsequent years were approximately $US4,600 per year for all cancer patients.

Effects of patients' covariates on annual direct medical costs

Table 4 shows the influence of baseline covariates of patients on the annual direct medical costs by category. The base case annual mean medical costs for a type 2 diabetes female patient belong to category 1, aged ≤75 years, who did not have cancer

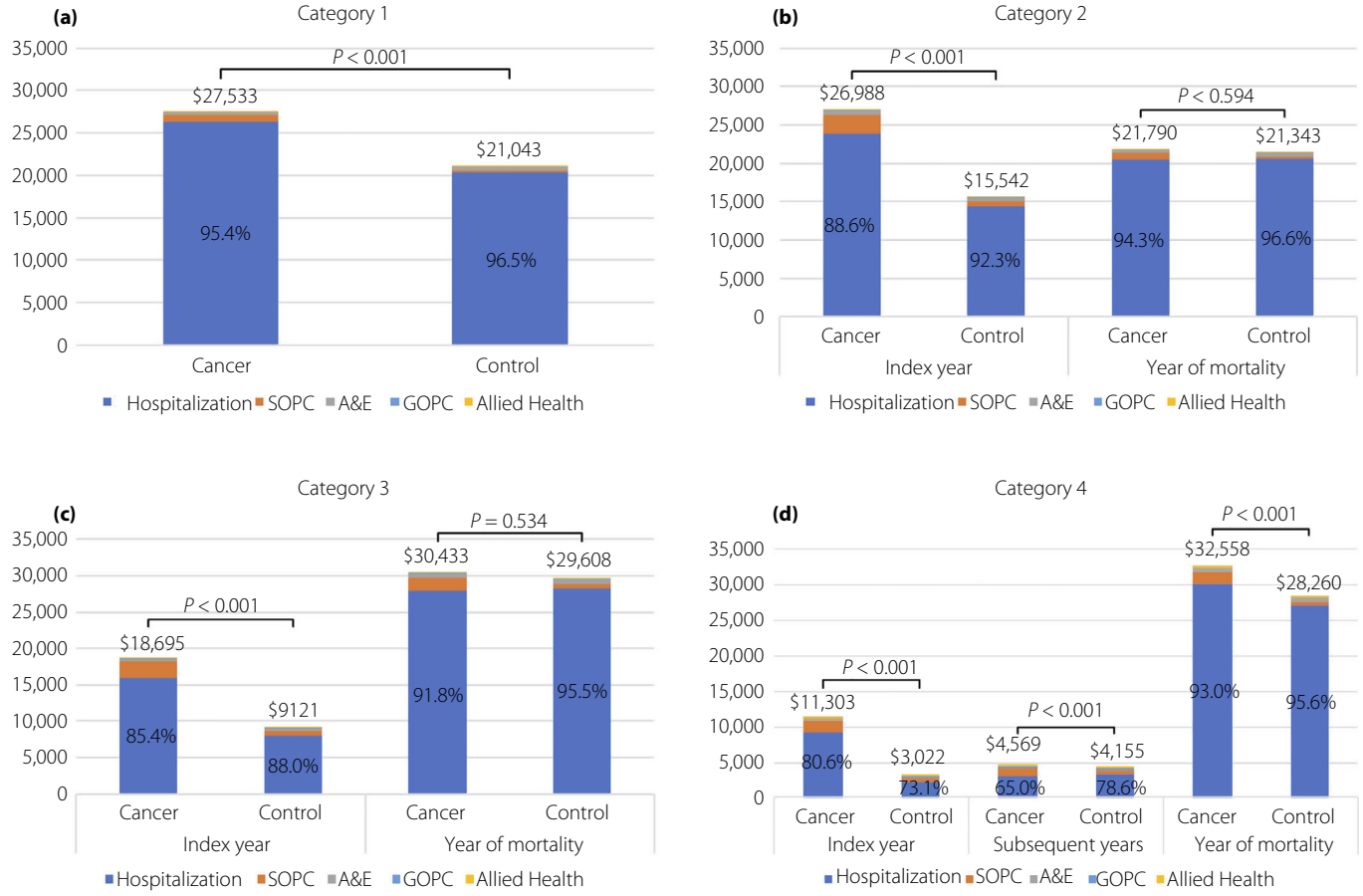

Figure 1 | Mean direct medical costs ($US) of patients, and proportion of costs attributed by hospitalization in the cancer and control groups in the index year, subsequent years and mortality year. A&E, accident and emergency department; GOPC, general outpatient clinic; SOPC, specialist outpatient clinic. Category 1: patients die in the index year; category 2: patients die in the second year after the index date; category 3: patients die in the third year after the index date; category 4: patients survive >3 years after the index date.

or other diabetic complications were $US14,366.22. Oncology patients incurred significantly greater medical costs than non-cancer patients, with a multiplier of 1.470 ($P < 0.001$). Medical costs were greater for patients aged ≤75 ($P < 0.001$). Compared with patients with a CCI ≤3, patients with a higher CCI had greater medical costs. The presence of gallbladder disease, end-stage renal disease and hypertension significantly increased the medical costs for patients in category 1, whereas the presence of other diabetic complications did not have a significant influence on annual costs. Of note, patients using insulin had significantly higher medical costs, whereas those taking oral antidiabetic drugs, antihypertensives or lipid-lowering agents had significantly lower costs.

The occurrence of cancer in patients of all other categories significantly increased the medical costs in the index year, subsequent years and the mortality years. Generally, a higher CCI, the presence of diabetic complications and the use of insulin increased annual medical costs, whereas the use of oral antidiabetic drugs, antihypertensives or lipid-lowering agents decreased them.

DISCUSSION

The present large-scale, population-based, cohort study estimated the direct medical costs and described the patterns of uptake of healthcare services by patients with both cancer and type 2 diabetes. This study also estimated the influence of characteristics of patients on direct medical costs and provided cost information of patients with specific tumors. The use of a propensity score-matching method enabled the cost comparison between cancer patients and control patients by using real-world data. The results of generalized linear models facilitated easy estimation of medical costs incurred by patients with different baseline characteristics.

The present study filled the research gap, and separately reported the medical costs incurred by type 2 diabetes patients with and without cancers by years. Several previous health

Table 3 | Mean direct medical costs ($US) with standard deviation of cancer patients in the diagnosis year, in the subsequent years and in the mortality year by sites of tumor

Sites of tumor	Category 1 (n = 4,811)		Category 2 (n = 1,377)			Category 3 (n = 725)			Category 4 (n = 9,956)			
	n (%)	Diagnosis year,$(US)	n (%)	Diagnosis year ($US)	Mortality year	n (%)	Diagnosis year ($US)	Mortality year ($US)	n (%)	Diagnosis year ($US)	Subsequent year ($US)	Mortality year ($US)
Lip, oral cavity and pharynx (N = 561)	97 (2.02)	42,066.32 (8,380.46)	46 (3.34)	32,085.96 (9,166.37)	28,072.39 (8,233.23)	31 (4.28)	28,572.1 (12,689.65)	32,069.94 (12,713.72)	387 (3.89)	18,429.11 (2,839.51)	4,287.77 (927.01)	31,820.49 (12,615.83)
Digestive organs including Esophageal, stomach, pancreatic, liver, gallbladder, colorectal, anal cancer (N = 5,843)	1,839 (38.22)	28,721.00 (1,199.82)	557 (40.45)	29,580.42 (2,385.92)	21,468.45 (1,831.32)	274 (37.79)	21,570.43 (2,682.81)	29,772.51 (3,089.45)	3,173 (31.87)	15,199.79 (576.63)	5,116.07 (394.76)	31,528.71 (3,072.53)
Respiratory system (N = 1,645)	690 (14.34)	24,539.40 (1,523.83)	196 (14.23)	20,745.52 (2,903.76)	22,755.97 (3,166.10)	92 (12.69)	14,907.88 (6,090.02)	27,270.16 (5,013.89)	667 (6.70)	10,403.65 (939.00)	4,929.98 (907.96)	24,753.09 (4,050.22)
Bone, skin, soft tissue and breast (N = 2,539)	98 (2.04)	30,130.23 (5,256.34)	106 (7.70)	19,988.01 (4,598.54)	18,484.26 (3,587.70)	74 (10.21)	11,253.2 (2,757.01)	28,080.38 (5,366.14)	2,261 (22.71)	7,133.32 (472.55)	3,694.90 (349.36)	30,714.18 (4,559.82)
Genitourinary organs including kidney, bladder, ureter, uterus, genitalia, prostate, and ovary (N = 3,071)	336 (6.98)	32,520.42 (3,049.85)	187 (13.58)	26,570.94 (4,161.12)	26,221.86 (4,265.75)	140 (19.31)	15,634.7 (2,854.77)	33,654.11 (4,513.94)	2,408 (24.19)	8,207.70 (467.62)	4,407.84 (352.36)	38,124.71 (4,988.48)
Lymphatic and hematopoietic tissue (N = 424)	110 (2.29)	41,647.28 (6,277.62)	40 (2.90)	33,762.93 (8,612.39)	18,893.08 (9,202.82)	18 (2.48)	28,706.56 (12,983.92)	39,598.94 (12,817.13)	256 (2.57)	16,653.34 (2,526.06)	5,681.45 (1,279.90)	36,635.21 (8,207.30)
Other and unspecified sites (N = 2,786)	1,641 (34.11)	24,478.15 (1,023.28)	245 (17.79)	27,372.49 (3,798.34)	19,087.67 (2,097.52)	96 (13.24)	19,249.16 (4,525.76)	30,220.68 (4,566.09)	804 (8.08)	12,538.97 (1,133.88)	5,045.94 (851.01)	31,544.20 (6,160.39)

Category 1: patients die in the index year; category 2: patients die in the second year after the index date; category 3: patients die in the third year after the index date; category 4: patients survive >3 years after the index date.

Table 4 | Effects of cancer and other baseline covariates on costs in the index year, subsequent years and year of death (generalized linear model with log link of gamma distribution)

Category 1 and 2

Covariates	Category 1			Category 2					
	Index year			Index year			Mortality year		
	Multiplier	95% CI	*P*-value	Multiplier	NA	*P*-value	Multiplier	95% CI	*P*-value
Constant	NA	NA	<0.001*	NA	(1.934, 2.359)	<0.001*	NA	NA	<0.001*
Cancer (vs non-cancer)	1.470	(1.386, 1.559)	<0.001*	2.136	(0.866, 1.068)	0.461	1.151	(1.064, 1.245)	<0.001*
Age >75 years (vs ≤75 years)	0.868	(0.822, 0.916)	<0.001*	0.961	(0.906, 1.099)	0.963	0.910	(0.839, 0.988)	0.025*
Male (vs female)	0.980	(0.934, 1.028)	0.412	0.998	(0.957, 1.156)	0.292	1.027	(0.953, 1.107)	0.487
Duration of T2DM > 5 years (vs ≤5 years)	1.006	(0.958, 1.056)	0.822	1.052	(0.398, 1.438)	0.394	0.955	(0.887, 1.028)	0.218
CCI (vs CCI ≤3)									
4–6	1.638	(0.970, 2.765)	0.065	0.757	(0.772, 3.056)	0.222	1.959	(1.298, 2.957)	0.001*
≥7	1.820	(1.062, 3.120)	0.029*	1.536	(1.136, 1.394)	<0.001*	1.824	(1.130, 2.945)	0.014*
Presence of cardiovascular disease	0.999	(0.949, 1.052)	0.973	1.258	(0.824, 1.390)	0.612	1.054	(0.976, 1.138)	0.182
Presence of mental health problems	0.990	(0.858, 1.141)	0.885	1.070	(0.905, 1.100)	0.962	0.986	(0.792, 1.227)	0.899
Presence of hyperlipidemia	1.015	(0.966, 1.066)	0.560	0.998	(0.959, 1.394)	0.127	0.978	(0.907, 1.054)	0.558
Presence of OSA	1.043	(0.936, 1.162)	0.449	1.156	(0.923, 1.279)	0.319	1.014	(0.875, 1.176)	0.850
Presence of gallbladder disease	1.100	(1.001, 1.208)	0.046*	1.086	(1.054, 1.293)	0.003*	0.982	(0.853, 1.131)	0.801
Presence of musculoskeletal and chronic orthopedic disorders	1.031	(0.976, 1.088)	0.279	1.167	(1.133, 1.428)	<0.001*	0.998	(0.919, 1.084)	0.958
Presence of ESRD	1.127	(1.049, 1.211)	0.001*	1.272	(0.895, 1.159)	0.776	1.196	(1.087, 1.317)	<0.001*
Presence of hypertension	1.154	(1.075, 1.239)	<0.001*	1.019	(0.959, 1.196)	0.222	1.157	(1.045, 1.280)	0.005*
Use of insulin	1.072	(1.014, 1.133)	0.014*	1.071	(0.649, 0.803)	<0.001*	1.111	(1.021, 1.209)	0.014*
Use of oral antidiabetic drugs	0.806	(0.768, 0.846)	<0.001*	0.722	(0.771, 0.935)	0.001*	0.797	(0.736, 0.864)	<0.001*
Use of antihypertensive drugs	0.821	(0.779, 0.865)	<0.001*	0.849	(0.826, 1.020)	0.113	0.775	(0.718, 0.836)	<0.001*
Use of lipid-lowering agents	0.849	(0.807, 0.894)	<0.001*	0.918	NA	<0.001*	0.856	(0.790, 0.927)	<0.001*

Category 3

Covariates	Index year			Mortality year		
	Multiplier	95% CI	*P*-value	Multiplier	95% CI	*P*-value
Constant	NA	NA	<0.001*	NA	NA	0.019*
Cancer (vs non-cancer)	2.478	(2.168, 2.831)	<0.001*	1.162	(1.069, 1.263)	<0.001*
Age > 75 years (vs ≤75 years)	0.899	(0.788, 1.026)	0.115	1.012	(0.928, 1.104)	0.783
Male (vs female)	0.939	(0.825, 1.069)	0.343	0.996	(0.923, 1.074)	0.912
Duration of T2DM > 5 years (vs ≤5 years)	0.961	(0.844, 1.094)	0.546	0.975	(0.904, 1.052)	0.512
CCI (vs CCI ≤3)						
4–6	2.522	(0.641, 9.921)	0.186	2.146	(0.877, 5.255)	0.095
≥7	8.075	(1.861, 35.035)	0.005*	2.961	(1.127, 7.778)	0.028*
Presence of cardiovascular disease	1.365	(1.196, 1.558)	<0.001*	1.099	(1.015, 1.19)	0.020*
Presence of mental health problems	0.839	(0.600, 1.172)	0.303	1.002	(0.842, 1.194)	0.980

Table 4 (*Continued*)

Category 3

Covariates	Index year			Mortality year		
	Multiplier	95% CI	*P*-value	Multiplier	95% CI	*P*-value
Presence of hyperlipidemia	1.007	(0.881, 1.150)	0.920	0.965	(0.894, 1.043)	0.372
Presence of OSA	1.235	(0.996, 1.53)	0.054	1.052	(0.912, 1.214)	0.487
Presence of gallbladder disease	1.294	(1.033, 1.621)	0.025*	0.985	(0.839, 1.155)	0.850
Presence of musculoskeletal and chronic orthopedic disorders	1.204	(1.042, 1.392)	0.012*	1.114	(1.018, 1.219)	0.019*
Presence of ESRD	1.338	(1.157, 1.547)	<0.001*	1.250	(1.142, 1.368)	<0.001*
Presence of hypertension	0.981	(0.842, 1.143)	0.807	0.983	(0.892, 1.083)	0.724
Use of insulin	1.092	(0.945, 1.261)	0.231	1.065	(0.977, 1.162)	0.152
Use of oral antidiabetic drugs	0.812	(0.705, 0.935)	0.004*	0.793	(0.726, 0.865)	<0.001*
Use of antihypertensive drugs	0.878	(0.771, 1.001)	0.052	0.841	(0.777, 0.909)	<0.001*
Use of lipid-lowering agents	0.890	(0.780, 1.016)	0.085	0.896	(0.824, 0.973)	0.009*

Category 4

Covariates	Index year			Subsequent years			Mortality year		
	Multiplier	95% CI	*P*-value	Multiplier	95% CI	*P*-value	Multiplier	95% CI	*P*-value
Constant	NA	NA	<0.001*	NA	NA	<0.001*	NA	NA	<0.001*
Cancer (vs non-cancer)	5.042	(4.857, 5.234)	<0.001*	1.352	(1.295, 1.412)	<0.001*	1.213	(1.136, 1.295)	<0.001*
Age > 75 years (vs ≤75 years)	1.267	(1.218, 1.318)	<0.001*	1.383	(1.343, 1.424)	<0.001*	0.909	(0.862, 0.959)	<0.001*
Male (vs female)	0.999	(0.961, 1.038)	0.961	0.990	(0.963, 1.019)	0.494	1.107	(1.059, 1.157)	<0.001*
Duration of T2DM > 5 years (vs ≤5 years)	1.129	(1.086, 1.174)	<0.001*	1.062	(1.032, 1.094)	<0.001*	0.949	(0.899, 1.001)	0.055
CCI (vs CCI ≤3)									
4–6	1.414	(1.218, 1.642)	<0.001*	1.287	(1.036, 1.600)	0.023*	0.960	(0.544, 1.693)	0.887
≥7	4.784	(3.788, 6.042)	<0.001*	1.331	(0.995, 1.781)	0.054	0.865	(0.457, 1.637)	0.655
Presence of cardiovascular disease	1.762	(1.693, 1.833)	<0.001*	1.527	(1.481, 1.575)	<0.001*	1.083	(1.035, 1.134)	0.001*
Presence of mental health problems	1.499	(1.359, 1.654)	<0.001*	1.351	(1.222, 1.494)	<0.001*	0.892	(0.773, 1.029)	0.118
Presence of hyperlipidemia	0.916	(0.879, 0.956)	<0.001*	0.881	(0.855, 0.907)	<0.001*	0.929	(0.885, 0.974)	0.003*
Presence of OSA	1.183	(1.099, 1.272)	<0.001*	1.128	(1.058, 1.203)	<0.001*	0.993	(0.894, 1.103)	0.893
Presence of gallbladder disease	1.333	(1.236, 1.438)	<0.001*	1.131	(1.064, 1.203)	<0.001*	0.986	(0.895, 1.086)	0.769
Presence of musculoskeletal and chronic orthopedic disorders	1.335	(1.280, 1.392)	<0.001*	1.209	(1.170, 1.249)	<0.001*	1.053	(0.996, 1.114)	0.070
Presence of ESRD	2.023	(1.875, 2.184)	<0.001*	1.723	(1.603, 1.852)	<0.001*	1.136	(1.056, 1.221)	0.001*
Presence of hypertension	1.063	(1.007, 1.122)	0.026*	1.080	(1.040, 1.121)	<0.001*	0.939	(0.888, 0.993)	0.028*
Use of insulin	1.503	(1.428, 1.582)	<0.001*	1.607	(1.553, 1.663)	<0.001*	1.127	(1.076, 1.181)	<0.001*
Use of oral antidiabetic drugs	0.669	(0.640, 0.698)	<0.001*	0.581	(0.563, 0.599)	<0.001*	0.753	(0.717, 0.791)	<0.001*
Use of antihypertensive drugs	0.770	(0.725, 0.817)	<0.001*	0.695	(0.668, 0.722)	<0.001*	0.874	(0.835, 0.915)	<0.001*
Use of lipid-lowering agents	0.860	(0.823, 0.898)	<0.001*	0.825	(0.801, 0.851)	<0.001*	0.893	(0.850, 0.938)	<0.001*

Category 1: base cost of index year, $US14,366.22; category 2: base cost of index year, $US18,306.62; base cost of mortality year, $US12,148.92; category 3: base cost of index year, $US3,446.30; base cost of mortality year, $US14,987.65; category 4: base cost of index year, $US1,818.00; base cost of subsequent years, $US3,612.85; base cost of mortality year, $US36,805.40. CCI, Charlson Comorbidity Index; CI, confidence interval; ESRD, end-stage renal disease; NA, not applicable; OSA, obstructive sleep apnea; T2DM, type 2 diabetes mellitus.
*$P < 0.05$ indicates statistically significant difference.

economic evaluations focused on the medical costs of either cancers or type 2 diabetes[12,13,27–30], but none had quantified the impacts of cancer on the direct medical costs and healthcare utilization among type 2 diabetes patients, given the intrinsic connections between the two diseases. In addition, few of them reported the medical costs separately by the diagnosis year, subsequent years and mortality year[28,31,32].

The present study also showed that greater medical expenditures were incurred in the mortality year. Of special note was that the total medical costs and inpatient costs of oncology patients with a remaining life expectancy >3 years had a U-shaped curve; that is, higher costs were incurred in the year of diagnosis and mortality, whereas costs were lower in the years in between. In comparison, the medical costs of type 2 diabetes patients without cancer showed an increasing trend over the years. Similar findings were supported by previous studies, which found that costs of cancer patients had a typical U-shaped curve, whereas medical costs of type 2 diabetes patients increased over time [28,31]. The increased medical costs in the mortality year were mainly because patients had more hospital stays in their last year of life than in the years preceding the mortality year. This finding was consistent with the observations of previous studies, which confirmed that patients with more hospital stays had a significantly greater chance of mortality[33]. Indeed, the present study showed that hospitalization accounted for most of the annual medical costs of patients over the years. A previous study also found that inpatient admissions contributed the largest part of the total medical costs for cancer patients, whereas costs for other services, such as chemotherapy and radiotherapy, accounted for no more than 10% of the total direct medical costs[16]. However, hospitalization costs ranged only from 38% to 64% of the total costs of oncology patients in Ontario[16], but accounted for up to 96% of the total costs for cancer patients in the present study. One possible explanation to this discrepancy is that patients who were enrolled in the present study were approximately 10 years older than those included in the Ontario study[16]. As the length of stay in hospitals generally increased with ages[34], a higher percentage of medical costs were attributed to hospitalization.

The direct medical costs and survival rates varied across tumor sites. For example, patients with cancers of the lip, oral cavity and pharynx, and those with lymphatic and hematopoietic cancers had relatively greatercosts than patients with other types of cancers. Compared with patients with survivable cancers, those with riskier cancers tended to have a short life expectancy. In our analyses, a great percentage (24.19%) of patients with genitourinary cancer survived beyond 3 years after cancer diagnosis, whereas a large portion (34.11%) of patients with cancer in other and unspecified tumor sites died within 1 year. These results had a message for policy makers to implement early health interventions, such as cancer screening tests, in type 2 diabetes patients to prevent cancers; and to provide patients who are at high risks of lower survivable and/or costly cancers with special care. Apart from sites of tumors, age is another important factor that affects the life expectancy after cancer diagnosis. Life expectancy in younger patients with cancer is expected to be longer than that of older patients in a same condition[35]. Indeed, patients in category 4, with a mean age of 74.6 years, were significantly younger than patients in categories 1–3 (Table S3). In addition, a greater percentage of patients in category 1 had multiple chronic diseases, which could shorten their life expectancy.

Apart from cancers, the presence of comorbidities was associated with increased healthcare expenditure. The present study suggested that patients who had a higher CCI, diabetic complications and used insulin tended to incur higher costs than patients with lower CCI, had no or fewer diabetic complications, and used oral antidiabetic drugs. This finding was consistent with previous studies that focused on the effects of comorbidities on medical costs in oncology patients[31,36,37]. For example, a costing analysis calculated the costs of elderly patients with neuroendocrine tumors found that a comorbidity score of ≥3 incrementally increased the monthly medical costs by $1,359 for patients who survived beyond 1 year, and $4,185 for patients who died within 1 year[31]. Also, comorbidity was found to contribute to higher medical costs for patients with colon, breast and prostate cancers[36].

This study showed the importance of involving cancer as one of the health states in diabetes economic models. The current guidelines for computer simulation modeling of diabetes and its complications provide general requirements on model construction, such as considering long-term horizons, including multiple complications and carefully selecting a perspective; but they do not specifically require the inclusion of cancer[19]. However, the reliability and validity of diabetes models are considered questionable if cancers are not incorporated as one of the modelled complications. It is not only because cancers deteriorate the quality of life and largely increase the medical costs of type 2 diabetes patients, but also because diabetes is associated with increased risks of different cancer types by 10–131%[9,10]. The findings of the present study, therefore, had implications for health economists in refining the current diabetes economic models, and can be used for future cost-effectiveness analyses of health interventions for type 2 diabetes.

However, several limitations should be acknowledged. First of all, cancer patients and non-cancer patients were not matched separately by categories, leading to imbalanced baseline characteristics of two groups in the same category. Also, cancer patients in category 1 had fewer matched patients, whereas those in category 4 had more matched cases. Second, the costs of healthcare services incurred in the private sector and the indirect costs as a result of the loss of productivity were not taken into consideration. In addition, the packaged charges of HA outpatient and inpatient services include pathology investigations, medication within the scale provided at the hospitals or clinics and other necessary examinations, but do not cover the costs of immunology therapies and surgical

operations. Therefore, the cost estimations of the present study might be underestimated. Third, this study assumed that patients enrolled from 2006 to 2017 incurred the same unit cost for each healthcare service, without making an adjustment for inflation over time.

To conclude, type 2 diabetes patients with cancers had higher direct medical costs than those who were cancer-free in the year of cancer diagnosis, the years that followed and the year of death. Hospitalization accounted for the majority of these direct medical costs.

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DISCLOSURE

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1 | Flowchart of the study.
Figure S2 | Pyramid of propensity score distribution among type 2 diabetes patients with and without cancers.
Figure S3 | Mean direct medical costs incurred in the index year and in the mortality year among type 2 diabetes mellitus patients with and without cancers

Table S1 | International Classification of Primary Care, Second Edition and International Classification of Diseases, Ninth Revision, Clinical Modification diagnosis codes.

Table S2 | Unit cost of healthcare services.

Table S3 | Baseline characteristics of type 2 diabetes patients with cancers in four categories.